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Principal Investigator: Jonathan E. Rhoads, M.D.

Subject: The Evaluation of Vasoactive Agents in Shock with and in the Absence of Intravenous Fluid Therapy.

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ABSTRACT

1. Preparing Institution: The University of Pennsylvania
School of Medicine
Harrison Department of Surgical Research

2. Title of Report: The Evaluation of Vasoactive Agents in Shock with and in the Absence of Intravenous Fluid Therapy.

3. Principal Investigator: Jonathan E. Rhoads, M.D.

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This report deals with a number of areas of study related to vasoactive agents and fluid therapy in shock:

A. The effects of beta-adrenergic receptor stimulation on blood flow, oxidative metabolism and survival in hemorrhagic shock.
   1. (Dose--response relationships in differing circumstances,
   2. Survival studies with continuous Isoproterenol infusion,
   3. Oxygen consumption and excess lactate with Isoproterenol).

B. Hepato-splanchnic lymph production with hydrocortisone treated endotoxin shock;

C. The ventilatory response to hemorrhage.
   1. (Alterations in the response of ventilation to carbon dioxide,
   2. Studies in awake animals,
   3. Carotid sinus denervation and vagal-sympathetic trunk division).

D. Dynamic alterations in the volume of distribution of anions in hemorrhagic hypotension and hypoxemia;

E. The hemodynamic and metabolic effects of lactated Ringer's solution in hemorrhagic shock.

A. The Effects of Beta-Adrenergic Receptor Stimulation on Blood Flow, Oxidative Metabolism and Survival in Hemorrhagic Shock.

Isoproterenol, a beta-adrenergic receptor stimulating drug was found in large doses to be beneficial for animals in hemorrhagic shock compared to saline control infusions. Giving the drug during severe hypovolemia (68% of estimated blood volume removed) increased cardiac output and oxygen consumption, substantially decreased the hematocrit suggesting better capillary refilling of the circulation, increased ventilation, tended to decrease the production of lactate, and in large doses increased mesenteric blood flow. This occurred with the mean arterial blood pressure maintained at 30 mm.Hg and without any of the shed blood being returned to the animals.

Survival was not decreased by any dose studied and tended to be better than controls with 2 µg/kg/min. This is in contrast to most studies showing decreased survival in hemorrhagic shock with vasoconstrictor drugs. The gastro-intestinal tract of the dog was protected by large doses of Isoproterenol, which increased mesenteric blood flow, even in animals which did not survive. The cause of death in animals not surviving treatment with the drug seemed to be respiratory insufficiency resulting from pulmonary atelectasis and consolidation with fibrinous material in the tracheobronchial tree. The cause for this was not determined but seemed to be increased tracheobronchial secretion.

Driving a hypovolemic circulatory system by an inotropic vasodilator agent was not harmful to the animal except for the respiratory complications. These should be preventable by keeping the tracheal bronchial tree free of secretions. This supports the physiologic appropriateness of Isoproterenol for the treatment of various forms of shock when it is required. Obviously it should not be required until any circulatory volume deficit is replaced as evidenced by a high or rising central venous pressure.

B. Hepato-splanchnic Lymph Production with Hydrocortisone Treated Endotoxin Shock.

This study has recently been completed and the data is being evaluated. Massive pharmacological doses of hydrocortisone were found to decrease peripheral resistance and increase cardiac output in traumatized and operated animals. With these changes lymph production was increased in the hepato-splanchnic bed. Following the infusion of endotoxin, lymph production was increased even more than in control animals but did not occur as rapidly after endotoxin injection. Survival time even in traumatized, operated animals receiving endotoxin was prolonged with hydrocortisone; however, survival was not increased in the animals studied because of the severe degree of trauma adding to the endotoxin indicating that this is a potentiating factor with endotoxin. This indicates that trauma plus sepsis potentiate each other in perpetuation or production of shock. This information also suggests that the role of hydrocortisone in protection against endotoxin and potentially in the treatment of septic shock lies in a rather nonspecific effect of decreasing vascular reactivity as a rather weak vasodilator agent.

C. The Ventilatory Response to Hemorrhage.

1. Alteration in the response of ventilation to carbon dioxide.
2. Studies in awake animals.
3. Carotid sinus denervation and vagal-sympathetic trunk division.

Increased ventilation with blood loss has been ascribed to baro- or chemoreceptor stimulation, metabolic acidosis or increased respiratory center PCO_2 or hydrogen ion concentration, or has not been found to occur. Awake, unsedated trained dogs with tracheostomies had respiratory rate, tidal volume, minute volume, O_2 consumption, right ventricular and systemic arterial pressures, arterial and mixed venous hematocrit, pH, PCO_2, PO_2, oxygen and carbon dioxide content, cardiac output and alveolar-arterial oxygen gradient, measured with bleeding at varying rates and in different positions to shock levels. Anesthetized dogs were studied with carotid body and sinus denervation and cervical vagus-sympathetic trunk division. In awake animals with 10% of estimated blood volume lost, tidal volume increased and respiratory rate decreased with minute volume unchanged. With 35% estimated blood volume loss, blood pressure decreased from 132 to 63, tidal volume and respiratory rate increased, minute volume increased 204%, arterial pH rose to 7.56 and PCO_2 fell to 22 mmHg. Marked hyperventilation and agitation quickly produced transient apnea. In anesthetized animals with 20% estimated blood volume loss and blood pressure from 141 to 115, minute volume increased 644%, arterial pH was 7.5, PCO_2 was 20 mmHg. Systemic metabolic acidosis was not present. Cardiac output was unchanged or decreased. At 30 mmHg ventilation became regular and slow with minute volume above control. Rapid bleeding produced no ventilatory stimulation in some animals. After carotid denervation, 20% estimated blood volume lost, increased minute volume 600%, as blood pressure fell from 181 to 126. After vagal-sympathetic trunk division 20% estimated blood volume loss increased minute volume 660% as blood pressure fell from 187 to 48 with continued hyperventilation at 20 to 30 mmHg blood pressure. Oxygen consumption increased initially with bleeding and then fell. Alveolar-arterial oxygen gradient rose with bleeding in anesthetized animals but decreased in awake animals. During blood return ventilation was unchanged in anesthetized animals but decreased in awake animals even with sodium bicarbonate given. Characteristic changes in ventilation with hemorrhage were found which were considerably different in awake and anesthetized animals. This ventilatory stimulation was not the result of baro- or chemoreceptor stimulation or metabolic acidosis. Alterations with vagal-sympathetic division and other factors suggest that this was a function of decreased cerebral blood flow. This response may be deleterious since the respiratory alkalosis observed would further reduce cerebral blood flow.

D. Dynamic Alterations in the Volume of Distribution of Anions in Hemorrhagic Hypotension and Hypoxemia.

Effects of hemorrhagic shock and hypoxemia on the physiologic control of the extracellular fluid compartment were studied in splenectomized dogs. With ureteral occlusion, volumes of distribution of radiosulfate and thiocyanate were measured for five hours and the second component of the dilution curve after two hours in control animals was compared with animals bled or made hypoxemic at two hours. The time rate of change of apparent volumes of distribution was found to be linear. Least squares analysis yielded rates of 334 ± 125µl/Kg/min. for sulfate, 114 ± 83µl/Kg/min. for sulfate after bleeding (difference 220 µl/Kg/min., $P < .01$); 30 ± 32µl/Kg/min. for SCN, control, 0 ± 43µ l/Kg/min. for SCN after

bleeding (difference 32 µl/Kg/min., P >0.1). The decreased rate of distribution of sulfate with no significant change in that of thiocyanate suggests that hemorrhagic shock did not produce fluid shifts into or out of the total extracellular compartment but did produce changes in movements of certain ions used to measure extracellular fluid. This effect must be considered in studying extracellular fluid with hemorrhagic shock. Hypoxemia produced little change in sulfate distribution.

E. The Hemodynamic and Metabolic Effects of Lactated Ringer's Solution in Hemorrhagic Shock.

Hemorrhagic shock in three groups of dogs was treated prior to irreversibility by Ringer's lactate solution alone, Ringer's lactate solution plus half the shed blood, or blood alone. Measurements included cardiac output, oxygen consumption, blood gas tensions and contents, pH, hematocrit and lactate, pyruvate and excess lactate levels. The total body metabolic deficit was adequately corrected by all three treatment programs indicating that an electrolyte solution given in sufficient volume was satisfactory in this respect for the treatment of severe hypovolemic shock. However, when Ringer's lactate solution was used alone to replace a large blood loss, normal oxygen consumption was maintained only by increased cardiac output as well as increased oxygen extraction and a low venous oxygen content. This would make the animal vulnerable to any further insult. Ringer's lactate solution given with blood decreased the volume of blood required in hemorrhagic shock to provide adequate cardiac output, oxygen consumption and blood gas contents along with correction of altered metabolism. Ringer's lactate solution in the volumes and rate given transiently increased cardiac output beyond the control value whereas blood did not. The buffered saline provided some immediate correction of metabolic acidosis but three hours after treatment there were no significant differences in any of the measured parameters in the three groups. Animals given Ringer's lactate solution plus half the shed blood had a normal hematocrit at the end of the study. Previously described beneficial effects of electrolyte solutions in addition to blood as compared to blood alone in the treatment of hemorrhagic shock seem to be due in part to better flow characteristics with hemodilution.

This study supports the clinical use of Ringer's lactate solution along with blood for the treatment of hypovolemic shock. It should be helpful not only in the initial emergency treatment of shock before blood is available but also along with blood to decrease the volume of blood necessary and for the other advantages which it may offer. The present report applies only to hypovolemic shock and not to other causes of hypotension. The study was carried out under controlled conditions with adequate ventilation and with the animal breathing 100% oxygen, in contrast to clinical situations with many uncontrollable variables. The potential danger of excessive hemodilution with reduced oxygen carrying capacity of the blood in spite of high blood flow or cardiac output must be recognized.

APPENDIX I

PUBLICATIONS:

1. Baue, A.E., Tragus, E.T. and Parkins, W.M. Effects of Sodium Chloride and Bicarbonate in Shock with Metabolic Acidosis.
American Journal of Physiology, 212:54-60, 1967.

2. Baue, A.E., Tragus, E.T. and Parkins, W.M. A Comparison of Isotonic and Hypotonic Solutions and Blood on Blood Flow and Oxygen Consumption in the Initial Treatment of Hemorrhagic Shock.
Journal of Trauma, September 1967.

3. Tragus, E.T., Parkins, W.M. and Baue, A.E. The Effects of Sequential Buffering, Extracellular Fluid Replacement and Hemodilution in Hemorrhagic Shock.
Surgery, 61:795, 1967.

4. Baue, A.E., Tragus, E.T., Wolfson, S.K., Jr., Cary, A.L. and Parkins, W.M. The Hemodynamic and Metabolic Effects of Ringer's Lactate Solution in Hemorrhagic Shock.
Annals of Surgery, July 1967.

5. Baue, A.E. Shock and Vascular Injury.
In Current Perspectives in Surgery, Hoeber Company, Philadelphia, in press.

6. Baue, A.E., Tragus, E.T. and Parkins, W.M. The Effects of Increased Osmolality and Correction of Acidosis on Blood Flow and Oxygen Consumption in Hemorrhagic Shock.
Journal of Surgical Research, August 1967.

7. Baue, A.E., Jones, E.F. and Parkins, W.M. Beta-Adrenergic Receptor Stimulation in Hypovolemic Shock.
Surgical Forum, Amer. Coll. of Surgeons, October 1967.

8. Baue, A.E., Crystal, R.G. and Parkins, W.M. Distribution of $^{35}SO_4$ and SCN during Hemorrhagic Shock and Hypoxemia.
Federation Proceedings, 26:267, 1967.

9. Crystal, R.G. and Baue, A.E. Dynamic Alterations in Volume of Distributions of Anions with Hypovolemia and Hypoxemia.
Submitted for publication, American Journal of Physiology.

10. Baue, A.E., Jones, E.F. and Parkins, W.M. The Effects of Beta Adrenergic Receptor Stimulation on Blood Flow, Oxidative Metabolism and Survival in Hemorrhagic Shock.
Submitted for publication, Annals of Surgery.

NOTE: Reprints of the above are being forwarded under separate cover. Those still in press will be forwarded when available.